Synaptic connectivity and short term plasticity in healthy and diseased brain: From rodents to humans

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Synaptic connectivity and short term plasticity in healthy and diseased brain: From rodents to humans

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door

Guilherme Silva
geboren te San Paolo, Brazilië

promotor:	prof.dr. H.D. Mansvelder
copromotor:	dr. R.M. Meredith

To my father

...

Heiße Magister, heiße Doktor gar
Und ziehe schon an die zehen Jahr
Herauf, herab und quer und krumm
Meine Schüler an der Nase herum –
Und sehe, daß wir nichts wissen können!
Das will mir schier das Herz verbrennen.

...

Faust, Johann Wolfgang von Goethe

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I

GENERAL INTRODUCTION

I

The human brain is the source of remarkable sensory, motor and emotional capabilities, giving rise to creativity, thought, movement, love and curiosity – it is also, however, at the core of many debilitating diseases. Neuropsychiatric and neurological diseases afflict and affect millions of human lives. It is estimated that 450 million people worldwide have a mental health problem (The world health report 2001, WHO Geneva) giving neuroscience research a clear incentive to understand the neurobiological underpinnings of brain disease. In order to describe, and ultimately understand in detail how the brain works, including how coding and storage of information takes place, a crucial step is to dissect this incredibly complex system into elementary parts that can be taken as the building blocks or fundamental constituents of the brain, and start by understanding processes at the level of neurons and connections between them.

Despite all we know about individual neuronal function, how millions of these cells wire together to generate brain function is poorly understood, even in lower mammals like mice and rats. Primates, and specifically humans, surpass all other mammals in intelligence (Roth and Dicke, 2012; Penn and Povinelli, 2007). The basis for this gain of function seems to be more than a simple increase in processing machinery, i.e. more neurons. It is thought that the neocortex and its subdivisions have endowed primates and humans with skills nonexistent among other species (Molnár & Clowry 2012; Deary et al. 2010). While all mammalian brains contain a similar basic wiring scheme from hindbrain to neocortex, there is a strong positive correlation between intelligence levels and neocortical volume, as well as neuronal packing density in the cortex. Primate taxa with higher intelligence levels display higher encephalization levels, i.e. increased brain mass relative to body mass and therefore more cortical neurons and synapses (Lefebvre 2012). Additionally, subtle changes in the synaptic processes that affect the transmission and storage of information are likely to contribute to the gain in performance seen in the primate brain. Little is known about the cellular and synaptic properties of human neuronal circuits. Focusing attention on the cellular and synaptic properties of the human neocortex that allow coding, transmission and storage of information will increase our understanding of brain function at a more fundamental level.

About a century ago, Ramon y Cajal (Cajal, 1911) outlined an approach that is still used today to study connectivity in the neocortex by staining and 'reconstructing' neurons outside the microscope. His methods revealed the complete structure of neurons, which he postulated to be the fundamental constitutional units of the brain. His techniques already revealed that neurons are organized and connected to form microcircuits that can be described as the building blocks of functional networks. In the mammalian neocortex, radially aligned 'sister cells' originating from the same mother cell within an ontogenetic clone, connect preferentially (Yu et al. 2009), forming specific microcircuits that are thought to constitute the functional columnar micro-architecture (Hubel & Wiesel, 1962; Mountcastle, 1957; Stepanyants et al., 2008) These small microcircuit networks, in their turn, connect to form a neocortical area. Diverse areas are engaged in different tasks from responses to and integration of primary sensory information to the storage of working memory, decision-making and other cognitive processes. (Douglas & Martin 1995; Douglas et al. 1995).

Despite several common underlying electrophysiological properties within groups of pyramidal neurons and groups of interneurons, such as active and passive neuron features

and synaptic time constants (Berger et al. 2009), neocortical areas that differ in function also show specialized organization for processing different types of information. Primary sensory areas, for example, are ordered in highly organized topological maps, tangential to the cortical surface (Woolsey & Van der Loos 1970; Petersen 2007). In contrast, areas where higher cognitive information is processed show distinct connectivity and layer-structure organization, segregating its projections into different output channels depending on the subcortical taget and the thalamic input (Morishima et al. 2011). Given the positive correlation between higher brain function and cortical volume, it may be that cortical synaptic organization and the specialization and subdivision of cortical areas is a direct product of evolution that equipped higher primates and humans with more efficient and capable brains.

At the cellular level, what are the important differences between the brains of different mammalian species? Are factors contributing to system complexity, i.e. the specialization and subdivision of cortical areas (Deary et al. 2010), cortical thickness (Choi et al. 2008), number of synapses (Rockland 2002), intra- and inter-cortical connectivity (Roth & Dicke 2012) and neuron spacking density (Roth & Dicke 2012), the aspects that endowed the human brain with special abilities? In other words, are the differences in computational power of the brain correlated to connectivity patterns between neurons and long range connections between brain areas, or are there evolutionary differences that can be observed at the system's building block that can account for the larger computational power (Emes & Grant 2012)? Answers to the above questions have not only philosophical implications but may also lead to the understanding of impaired information processing and brain disorders, such as mental retardation or the diverse forms of autism spectrum disorders (ASD).

The primary role of the brain is the encoding and storage of information, obtained through sensory perception or higher order cognitive processes, to guide a behavioral output. The main strategy, implemented by evolution in the central nervous system (CNS), to encode and transmit information, is proposed to be synaptic plasticity (Silberberg et al. 2004; Markram & Tsodyks 1996). Synaptic plasticity is the modulation of synaptic strength leading to enhancement or depression of the functional response. It is present in all types of synapses and is characterized by short-lived or long-lasting processes (Markram et al. 2011; Zucker et al. 2002). Plasticity comes in different flavors, categorized by its temporal properties: from short term plasticity (STP) (Fioravante et al. 2011; Zucker et al. 2002) to long term potentiation (LTP) or depression (LTD) (Zilberter et al. 2009), The phylogenesis of synapses, or the evolution of mechanisms in the synaptic machinery (Ryan & Grant 2009) that implemented features such as synaptic depression and facilitation, short and long lasting, is a strong indicator that systems evolved hand-in-hand with basic synaptic components, to optimize information flow within a network in the nervous system. It is one of the goals of this thesis, to assess, via experiments and modeling, how short term plasticity affects information encoding in the brain and how this feature evolved by direct comparison of rodent with human neurons. In chapter 2 of this thesis, I will directly address the question of whether excitatory connections between principal cells in the human neocortex may also use dynamic synapses as a strategy to code information and confront the measured values with numbers extracted from neocortical rodent synapses.

LONG TERM PLASTICITY IN RODENTS AND HUMANS: A BRIEF SURVEY

The history of long term plasticity, the concept of long lasting changes in the amplitude of synaptic responses, dates back from the first half of the twentieth century (Lloyd 1949; Larrabee & Bronk 1947). The modern view of plasticity, however, or the unification of concepts and ideas that lead to a more comprehensive view of the relationship between synaptic strength and learning and memory builds on the ideas put forward by the Polish neurophysiologist Konorski (Konorski 1948) and by the Canadian neuropsychologist Donald Hebb (Hebb 1949).

Hebb postulated that memories could be stored in assemblies of connected neurons, where the repeated drive of activity in a specific cell had a causal relationship with the activity in the driving cell, thereby strengthening their connection. This would then couple specific groups of neurons together and mould networks according to past experience (Hebb 1949), forming the substrate for memory storage. The first experimental observation substantiating, at the cellular level, Hebb's predictions came in 1964, when Kandel and Tauc paired an EPSP with a conditioning stimulus in the giant marine snail Aplysia, causing facilitation of the postsynaptic response (Kandel & Tauc 1964) and coupling this observation to the gill withdrawal reflex associative learning. Following the pioneering study of Kandel and Tauc a host of laboratories to even this day, dedicate their research efforts to understand the formation and storage of memory related to long-lasting changes in synaptic efficacy (Frégnac et al. 1988; Maren 2005; Rodrigues et al. 2004), coupling behavioral studies to cellular electrophysiology.

Up until the 1990s, LTP and LTD had only been observed by applying extracellular electrical stimuli to input fibers to neurons. It is obviously difficult to avoid hetero- and polysynaptic effects as well as effects of neuromodulators that might be accidentally released by stimulating the wrong afferents. In 1991 Roberto Malinow reported, for the first time, evidence of homosynaptic plasticity in monosynaptically-connected pairs of pyramidal cells in CA3-CA1 acute hippocampal slices (Malinow 1991). This paved the way for Henry Markram, in the laboratory of Bert Sakmann, to demonstrate that the relative timing of spikes emitted by pre- and postsynaptic neurons at monosynaptic connections between pairs of neurons in the neocortex, determined direction and magnitude of synaptic efficacy change (Markram 1997). The logical following experiment was to explore the time window inside which the order between pre- and postsynaptic neurons would cause lasting changes and how sharp was the switch between LTP and LTD. These measurements were made in 1998 by Guo-qiang Bi, Li Zhang and Mu-ming Poo (Bi & Poo 1998; Zhang et al. 1998). By performing paired recordings in dissociated neuronal hippocampal cultures, Bi and Poo mapped the coincidence time window between pre- and postsynaptic activation necessary to observe synaptic changes. They found a 40ms long window and a sharp transition between LTP and LTD with a 1ms precision. The phenomenon above described, was later baptized spike timing-dependent plasticity (STDP) (Song et al. 2000).

The majority of STDP studies have been carried out *in vitro* in brain slice preparations of cortex or hippocampus (Malinow 1991; Debanne et al. 1994; Markram 1997; Bi & Poo 1998). *In vitro* preparations are ideal for dissecting mechanistic aspects from a phenomenon, providing

experimental control of several variables. Ultimately, however, the physiological relevance has to be verified *in vivo* and naturally, in the human brain to validate if STDP is a potential mechanism underlying human learning and memory . Evidence of STDP occurrence *in vivo* was demonstrated in rodents and cats (Yao & Dan 2001; Schuett et al. 2001; Allen et al. 2003; Celikel et al. 2004; Jacob et al. 2007). In the human brain, however, evidence of STDP at the cellular level, had never been previously demonstrated. Up until recently, all available indications reporting the existence of STDP in the human central nervous system (CNS) came from experiments using paired associative stimulation (PAS)(Stefan et al. 2000). The method consists in pairing electrical stimulation of the peripheral nervous system with transcranial magnetic stimulation (TMS) and measuring the strength of motor evoked potentials (MEPs). The paradigm revealed Hebbian-like rules (Stefan et al. 2000; Wolters et al. 2003) suggesting the existence of STDP-like mechanisms governing PAS. However, the question remained 'can synapses in the human brain change strength in response to timed pre- and postsynaptic activity?' In this thesis, we set out for a proof-of-principle study, verifying the existence of STDP in acute human hippocampal slices (see chapter 3).

SYNAPTIC SHORT-TERM DYNAMICS AND INFORMATION CODING

Synaptic transmission is a dynamic phenomenon, such that the post-synaptic response contains information about the temporal structure of the pre-synaptic activity. Therefore, individual responses relate to the history of the preceding presynaptic spike train. Dynamic changes in synaptic transmission were first demonstrated 70 years ago (Feng 1941; Eccles et al. 1941) and still constitute a topic of active research (Schneggenburger et al. 2002; Sakaba 2008; Neher & Sakaba 2008). In most synapses, multiple plasticity processes are present, and the resultant modulation is a combination of facilitation and depression, in which the synaptic response is dependent on timing but also on a number of external agents such as concentration of exogenous ions and neuromodulators. Curiously, different synapses in the same species or brain regions, and even different terminals stemming from the same presynaptic neuron, can show different amplitudes of facilitation and depression, depending in part on the type of postsynaptic partner neuron (Markram et al. 1998; Varela et al. 1999; Koester & Johnston 2005).

The most relevant mechanistic regulators of synaptic plasticity are of presynaptic origin and among all of them is calcium concentration. Action potentials generated at the axon initial segment, spread along the axon, opening voltage-gated Ca^{2+} channels that, entering the presynaptic terminal, trigger the rapid release of vesicles containing neurotransmitters. There is a positive correlation between elevation in $[Ca^{2+}]_i$ and synaptic potentiation and also recovery from depression. Preventing increases in $[Ca^{2+}]_i$ by buffering presynaptic $[Ca^{2+}]$ (Regehr et al. 1994; Atluri & Regehr 1996; Feller et al. 1996)$_i$ or reducing $[Ca^{2+}]_i$ influx (Zengel et al. 1993), reduce short term facilitation. Furthermore, for some preparations, the elevation of presynaptic $[Ca^{2+}]_i$, accelerated the recovery from depression (Dittman & Regehr 1998; Wang & Kaczmarek 1998; Stevens & Wesseling 1998).

Another relevant parameter that modulates synaptic plasticity is the ionotropic autoreceptor (MacDermott et al. 1999; Turecek & Trussell 2001; Schmitz et al. 2001). The consequences of

activation of presynaptic cationic ionotropic receptors can be twofold. It depolarizes the presynaptic terminal causing either facilitation or depression of synaptic release. Facilitation happens when depolarization causes an increase in presynaptic $[Ca^{2+}]_I$ levels. The increase can happen either due to Ca inflow via ionotropic receptors permeable to calcium or through opening of voltage-gated Ca channels. Depression, on the other hand, happens when depolarization is subthreshold, and causes inactivation of voltage-gated Na and/or Ca channels.

Other factors are known to affect synaptic release such as, G-protein-linked (metabotropic) presynaptic autoreceptors (Miller 1998) and postsynaptic receptor desensitization (Jones & Westbrook 1996; Otis et al. 1996). Metabotropic receptors may inhibit the $[Ca^{2+}]_I$ level at the presynaptic terminal, or activate presynaptic K channels, reducing, thereby, the effectiveness of the AP or modulating, directly, a series of biophysical mechanisms responsible for neurotransmitter vesicle release machinery. Postsynaptic receptor desensitization, on the other hand, constitutes in the closing of ligand-gated channels with the agonist still bound. Its role in synapse strength modulation is complex, changing efficacy, in different time-scales, depending on the desensitized ligand.

The principles described above, give rise to the intricate machinery that governs the modulation of synaptic amplitude and recovery from synaptic depression and facilitation. The quantification and phenomenological description of this parameters lead Henry Markram and Misha Tsodyks to develop, a now widely-used protocol to study changes in synaptic plasticity, during the 1990s (Markram & Tsodyks 1996). A train of action potentials and a recovery pulse that could unravel not only changes in synaptic efficacy but also changes in the short term dynamics of synapses. By means of this protocol, they described the redistribution of synaptic efficacy or the notion that long lasting changes in synaptic strength also lead to modifications in short term dynamics. In parallel to that, they developed a phenomenological model that describes synaptic dynamics by assigning differential equations to changes in available synaptic resources (Tsodyks & Markram 1997; Markram et al. 1998). This model is central to the development of the present thesis and will be described, heuristically, in the next paragraphs and in more detail, at the end of this introduction..

Monosynaptic connections between neocortical principal cells, the main focus of the present study, areon average mediated by 5 to 8 synapses (Kalisman et al. 2005). Wetherefore set out to apply a model for short term synaptic plasticity to our data that could account for the overall effect of a set of synapses present in a postsynaptic response and allowed to attribute measurable parameters to our traces (Markram & Tsodyks 1996; Tsodyks & Markram 1997; Abbott et al. 1997).

A connection can, therefore, be described by its absolute amount of resources,

$$R + E + I = 1$$

where R(recovered, ready-to-use), E(effective, in-use) and I(inactive, just-used, not-ready) denote the fraction of the limited resources available to the synapse or set of synapses. If a presynaptic AP consumes all resources, this would generate the maximal possible response, defined as the absolute synaptic efficacy (A_{SE}). Each presynaptic AP recruits a fraction of resources from the recovered state(R), transitioning to a state E that inactivates to a state I with

a time constant τ_{in} and recovers back to state R with a time constant τ_{rec}. The biophysical process that occurs in the synaptic cleft is, in this phenomenological model, simplified in the different variables that describe the dynamics of the system. We assume that the processes replenishing the resources are slow and occur at a time scale τ_{rec}. The processes of activation of ready-to-use resources are infinitely fast, and occur only during the presynaptic action potential. Inactivation, or the time constant of transition between states E and I is also fast, but slower than activation.

Solving the differential equations that describe the dynamics of the three variables, R, E and I, and fitting the fixed parameters to experimentally obtained postsynaptic responses, gives, ultimately, five numbers that describe the underlying dynamics of the synaptic resources. The constants are A, for absolute synaptic efficacy, U for utilization of synaptic efficacy (proportional to the probability of release), τ_{rec} or the recovery from depression, which describes the recovery from, but also the time course of, depression. $\tau_{in,}$ usually disregarded since it is a very small time constant, and τ_{fac}, which is the time constant of facilitation (when the synapses display a facilitating component). From the post synaptic response, one can also extract the membrane time constant which is a passive property, usually taken into account when studying synapses with the Tsodyks-Markram model.

The above-derived model was successfully applied, throughout the thesis, to characterize and quantify different aspects of dynamic synapses in rodent and human neocortex. It is a phenomenological model, therefore an approximation to more intricate biophysical mechanisms that are sometimes condensed into one single variable. For a more detailed and mathematically complete derivation of the model, see technical excursus at the end of this introduction.

INFORMATION THEORETICAL FORMALISM

Synaptically-connected pairs of neurons make use of short term dynamics to encode information (Tsodyks & Markram 1997; Markram et al. 1998). Facilitation and depression are, therefore, features of the nervous system to convey and filter messages between neurons. Modifying the properties of short term depression and/or facilitation is a strategy to change the content conveyed by a synaptic connection. To describe information flow in a system where two communicating parties are sending and receiving content via a common channel, the best available tool is Information theory - a mathematical formalism developed during the 1940s (Shannon 1948). This theory sets out to quantify and measure information transduction and reliability between source and receptor. In data in this thesis, I consider this to be a pair of synaptically-connected neurons, representing a minimal functional microcircuit in the brain.

Information theory was originally developed by C.E. Shannon (Shannon 1948) while working for Bell Labs. Based on original works of Harry Nyquist (Nyquist, 1928) and Ralph Hartley (Hartley, 1928), Shannon developed an extensive mathematical formalism to describe/quantify information flow in a communication system, in particular in the presence of noise. With a 'communication system', Shannon referred to a five-fold scheme,

i) Information source, producing the message or sequence of messages to be conveyed to the receiving terminal. The message can be of various forms, a single function of time or several

functions of several variables. In our particular case, the presynaptic neuron, encoding a message that can be a single function of time or a function of external modulators, where the system is embedded.

ii) a transmitter, operating on the message making it suitable for transmission. In our case, the axon.

iii) the channel, or the medium for signal transmission, the synaptic cleft.

iv) the receiver, and inverter that reconstructs the operation done by the transmitter, the dendrites.

v) the destination, the object for which the message was intended, the postsynaptic cell-body.

For computational purposes, we will consider that communication between neurons connected via dynamic synapses happens in a discrete manner and follows the scheme developed by Gallit Fuhrman (Fuhrmann et al. 2002).

In the heart of information theory, lies a quantity that measures how much information is produced in a process, or the rate at which the information is produced. The measure was a concept initially borrowed from statistical physics, originally developed to study energy transfer in gaseous systems. Quantities of the form $H = -\sum p_i log p_i$ are central in the formalism of information theory. They measure information, choice and uncertainty, where p_i is the probability of finding a system being in cell i of its phase space.

The entropy of a system is, therefore,

$$H(X) = -\sum_{x \in \mathrm{X}} p(x) log_2 p(x)$$

and the conditional form,

$$H(X|Y) = \sum_{y \in \gamma} p(y) H(X|Y = y) = -\sum_{y \in \gamma} p(y) \sum_{x \in \mathrm{X}} p(x|Y = y) log_2 p(x|Y = y)$$

Mutual information is thus, defined, $I(X,Y) = H(X) - H(X|Y)$, if X is the postsynaptic response (PSR) and Y the preceding presynaptic interspike intervals or the known probability of synaptic release (P_r) it becomes possible to calculate the information content and rate in a pair of synaptically-connected neurons.

This formalism has been used by the group of Tsodyks (Fuhrmann et al. 2002) to verify whether encoded information depends on the frequency of presynaptic spikes and what the dependence of information on the phenomenological parameters of the synapses is (as extracted by the model of Tsodyks and Markram). They found that neocortical depressing and facilitating synapses have an optimal frequency where information transfer is maximal and that this frequency is a direct function of the biophysical parameters. In chapter 2 and in the general discussion, we make use of the same formalism to ask the question whether synaptically-connected pairs of neocortical neurons in the human brain can transfer more information than a synaptically-connected pair in the murine brain.

I

AUTISM, MENTAL RETARDATION AND INFORMATION TRANSFER AT SYNAPSES

Connections between neurons in the cortex and other brain areas are formed and refined during early years of our lives (Casey et al. 2005). In autism, which has an onset in early childhood, development of neuronal connections and synapses is disturbed (Just et al. 2012). Abnormalities in dendrite and spine structure are found in both patients suffering from autism and genetic mouse models of autism (Purpura 1974; Meredith et al. 2012).

Autism is a heterogeneous neurodevelopmental disorder of unknown aetiology that affects more than 1% of the population (Silverman et al. 2010; Auerbach et al. 2011). The diagnosis of autism depends on a 'triad' of deficits comprising impaired social interaction, impaired communication and restricted interests and repetitive behaviors (Belmonte & Bourgeron 2006). Autism is the extreme of a spectrum of abnormalities whose milder variants include Asperger syndrome, where language is intact but social and communicative inflexibility and restricted and repetitive interests and behaviors remain. The combination of this broad variation of phenotypes and a high rate of concordance in monozygotic twins of 90% suggests a large number of genetic and environmental biasing factors (Belmonte et al. 2004; Silverman et al. 2010; Minshew & Williams 2007). Considerable efforts are now focused on understanding the genetic causes of autism and using the genetic findings to select rational targets for effective treatments (Geschwind 2011). Synaptic development genes implicated in autism include neurexins, neuroligins, shanks, reelin, integrins, cadherins and contactins. Signaling, transcription, methylation and neurotrophic genes implicated in ASDs include phosphatase and tensin homologue (PTEN), MET, engrailed 2 (EN2), methyl-CpG-binding protein 2 (MECP2), fragile X mental retardation 1 (FMR1), tuberous sclerosis 2 (TSC2), L type voltage-dependent calcium channel, alpha 1C (CACNA1C), ubiquitin ligase E3A (UBE3A), Ca2+-dependent activator protein for secretion 2 (CADPS2) and brain-derived neurotrophic factor (BDNF). Neurotransmission genes, including the serotonin transporter, oxytocin and vasopressin receptors and GABA (γ-aminobutyric acid) receptor subunit β3, have been repeatedly associated with autism or highly implicated in social and affiliative behaviours impaired in autism (Silverman et al. 2010; Abrahams & Geschwind 2008). Interactions between multiple genes most likely cause "idiopathic" autism and epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits (Geschwind 2011; Muhle et al. 2004).

Genetic disorders caused by single gene mutations that are associated with ASD, such as Fragile X Syndrome (FXS) and Tuberous Sclerosis Complex (TSC), underlie a small proportion of ASD cases. Still, FXS is the most common genetic cause of ASD, and TSC and FXS together account for 6 to 10% of ASD cases (Belmonte & Bourgeron 2006). Estimates of the prevalence of autism in FXS range from 15% to as much as 60% (Belmonte & Bourgeron 2006; Budimirovic & Kaufmann 2011), and 20 to 60% of individuals affected by TSC are diagnosed with ASD (Ehninger & Silva 2011; Bolton et al. 2002). FXS and TSC are also characterized by cognitive delay and intellectual disability, which is also common in autism. It has been estimated that over 50% of autism patients also have intellectual disability (Newschaffer et al. 2007). Genetically defined

syndromes with increased prevalence of autism and intellectual disability offer an opportunity to understand the brain pathophysiology that manifests as ASD and intellectual disability. This knowledge can suggest potential therapies for autism, potentially also for non-syndromic cases, which represent the majority of autism cases (Belmonte & Bourgeron 2006; Budimirovic & Kaufmann 2011; Auerbach et al. 2011). Mouse models of these genetically defined disorders, which carry the same genetic mutations as human patients, have fuelled many breakthroughs in our understanding of these disorders over the past two decades (Budimirovic & Walter E Kaufmann 2011; Silverman et al. 2010; Auerbach et al. 2011).

Although autism diagnosis is currently based on purely behavioural criteria and symptoms may be uniquely human, genetic mouse models of ASD capture important behavioural features of ASD. The majority of mouse models with mutations in the genes identified to be associated with ASD listed above show ASD-like behavioural impairments (Silverman et al. 2010). For instance, Shank2 mutant mice carrying a mutation identical to the ASD-associated microdeletion in the human SHANK2 gene exhibit ASD-like behaviours including reduced social interaction, reduced social communication by ultrasonic vocalizations, and repetitive jumping. Both FXS (fmr1-/-) and TSC (tsc1/2+/-) mice show social impairments (Silverman et al. 2010; Auerbach et al. 2011; Bureau et al. 2008). Social approach behaviour is altered in both mouse models and they show reduced reciprocal social interactions (Silverman et al. 2010). What the neurobiological mechanisms are that lead from gene defect to behavioural phenotype in ASD is poorly understood.

Studying information transfer and coding in healthy rodent and human neocortex gave estimates and values as to how effectively a connection between two cells can code and transmit information as a function of the synapse's biophysical parameters. The next logical step would be to probe the validity of this findings either by pharmacologically altering the biophysical parameters of the synapses or by applying the same experimental/theoretical paradigm to an impaired cortical network, i.e. one where efficiency in coding and/or transmission of information, may be affected. Among the possible test frameworks we have chosen to study two established models for mental retardation and autism. The fragile X model (chapter 4) where the deletion of a single murine gene is responsible for producing a phenotype analog to the human syndrome and the valproic acid (VPA) model (chapter 5), that mimics in utero exposure to a teratogen, inducing the autism phenotype.

Development of cognitive function requires the formation and refinement of synaptic networks of neurons in the brain. Mental retardation is characterized as a deficit of cognitive abilities and is thought to affect 2-3% of the worldwide population (WHO 1997 (Chiurazzi & Oostra 2000)). A unifying pathological feature across both syndromic and non-syndromic forms of mental retardation is abnormal synaptic spine morphology on neurons in the brain (Kaufmann & Moser 2000; Ramakers 2000). Spine pathologies in retardation syndromes are seen throughout the brain and are already present during early postnatal stages of development, before significant cognitive and behavioral impairments are observed(Purpura 1974). However, it is not yet clear whether these synaptic pathologies translate into alterations in functional connectivity at microcircuits within a cortical region or indeed at the neuronal network level across the brain.

Fragile X syndrome, the most common form of inherited mental retardation, is caused by mutations in the X-linked Fmr1 gene leading to a decrease or absence of Fragile X mental retardation protein (Verkerk et al. 1991; Jin & Warren 2000). Both humans and the corresponding transgenic mouse model, the Fmr1-KO mouse show characteristic spine morphology abnormalities in many regions in the brain (Nimchinsky et al. 2001; Comery et al. 1997; Irwin et al. 2000). Despite similar abnormalities in synaptic morphology in frontal cortex (Meredith et al. 2007), it is not known how this translates into altered patterns of synaptic connectivity in cortical neuron networks. On a network level, both humans with Fragile X syndrome and Fmr1-KO mice show increased susceptibility to epileptic seizures, suggesting an imbalance in excitatory/inhibitory activity in neuronal circuitry (Wisniewski et al. 2012 ; Chen & Toth 2001). Findings in sensory neocortex support such an idea with longer duration of UP state network activity in the Fmr1-KO mouse, thought to be underpinned by a decrease in excitatory drive on to fast-spiking neurons and increased hyperexcitability of excitatory neurons (Gibson et al. 2008). A transient change in excitatory connectivity between layers 4 and 2/3 in the barrel cortex has also been reported in the Fmr1-KO mouse (Bureau et al. 2008) although this was transient, occurring during a critical developmental period. Evidence of alterations in hippocampal glutamatergic short term synaptic dynamics have been previously reported (Pilpel et al. 2009; Deng et al. 2011), as well as evidence relating presynaptic alterations in specific synaptic proteins (Nueroligins, Neurexin1 and Cadherins 8-10) to autism (Südhof 2008; K. Wang et al. 2009; Pagnamenta et al. 2011)., however, the open question as to whether fine changes in the temporal structure of presynaptic signals might be detected and whether or not these alterations are related to possible impairments in the synaptic machinery. In chapter 4 of this thesis, we quantified and modeled the effects of differences in recovery from synaptic depression that might result from the delayed maturation of spines in the Fmr1-KO mouse.

Current theories for developmental disorders of autism and mental retardation such as Fragile X syndrome, propose models of disordered connectivity at the network level based upon functional neuro-imaging studies and micro-structural measures of neuronal density and spine pathology (Belmonte & Bourgeron 2006; Rippon et al. 2007). Furthermore, there is clinical evidence, leading to the hypothesis of local hyperconnectivity and long range hypoconnectivity (Belmonte et al. 2004). Dendritic spines receive the vast majority of excitatory synaptic contacts in a network. In chapter 4 of this thesis we tested whether the increase in dendritic protrusions as observed in synapse morphology in Fragile X syndrome, would lead to a functional hyperconnectivity between excitatory neurons. Furthermore, as the presence of immature spines in the developed Fragile X brain may suggest, in chapter 4 of this thesis we tested the hypothesis that these spine alterations may lead to impaired functional properties of synaptic connections, by examining connectivity properties in principal cells of layer 5 in the mPfC and dynamic properties inherent to the synapses. Short term synaptic plasticity evolves with development (Etherington & Williams 2011) and the full understanding of neurodevelopmental disorders relies on identifying the time window(s) in which the alterations responsible for the disease's phenotype can be first identified (Wolff et al. 2012). Therefore, in this thesis, we also examined the temporal development of synaptic properties in the mouse model for Fragile X syndrome.

Diverse genetic and chemical -induction animal models of autism have been used to study autistic disorder phenotypes at synaptic and behavioral levels(Williams & Casanova 2011). In addition to studying the Fragile X model for mental retardation and autism (chapter 4), we focused on studying synaptic dynamics/ connectivity in a teratogenic animal model of autism(chapter 5). The valproic acid (VPA) model is based on *in utero* exposure of the foetus to the short chained fatty acid VPA, which has been used to treat bipolar disorders, epilepsy and migraine in pregnant women. If administered to humans during specific trimesters of pregnancy, it results in 60% of cases where offspring exhibit two or more autistic traits and in 11% of the cases, a classic diagnosed form of autism (Moore et al. 2000). Henry Markram's group (Rinaldi et al. 2007) used the VPA model of autism in rats, developed by PM Rodier (Rodier et al. 1996), to study the underlying synaptic and neuronal changes following exposure to VPA. Their findings led to publication of a theory called "Intense world syndrome", to propose an explanation of neurobiology underlying autism and autistic spectrum disorders (Markram & Markram 2010). The theory proposes the hyper-reactivity and hyper-plasticity of local neural microcircuits as the leading cause to autism spectrum disorders. Resulting in hyper-perception, -attention, -memory and –emotionality. It is, however, relevant to mention that these conclusions were founded on observations made in VPA treated rats at one specific developmental window. In this thesis (chapter 5), we extended the initial study of T Rinaldi(Rinaldi et al. 2007), using the same experimental paradigm applied by JV Le Be (Le Bé & Markram 2006) to study microcircuit plasticity. Furthermore, we quantified the synapse's biophysical parameters and asked the question: does VPA treatment on the change in strength of connections and probability of release as a function of somata distances?

AIMS OF THIS THESIS

As described above, neocortical microcircuits, or pairs of synaptically connected neurons, make use of changes in synaptic efficacy depending on the temporal structure of the presynaptic cell firing pattern. These changes can be short or long lasting and are a feature of the CNS employed to code and store information. Using the formalism of classical information theory, coupled to a biophysical model of dynamic synapses, it is possible to quantify the information content in a pair of connected neurons. Hence parameters from dynamic properties of synapses have a direct effect in the boundary conditions for information coding and storage. Therefore, we aim to measure and test the limits of information coding related to connectivity and synaptic dynamics in human, murine, healthy and diseased neocortical tissue.

To reach this aims we used multipatch intracellular paired recordings to quantify connectivity rates and measure/model synaptic properties in diverse frameworks. In doing so, the following research questions were addressed:

1. How does short term synaptic depression influences information coding in human cortical synapses? In chapter 2 we directly measured and compared dynamic properties of human neocortical excitatory synapses. We verified and compared the synaptic response to a train of Poisson stimuli as well as tested whether human cells can track fine temporal features conveyed by mimicking upstream synaptic activity. Furthermore, based on synaptic

properties and using information theory, we calculated the maximum information content and transfer rate in a human and rodent excitatory synapses.

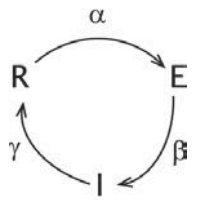
2. Is it possible to induce, at a cellular level, long term synaptic plasticity in the human brain? The formation and maintenance of memories is proposed to correspond to the brain's ability to maintain long-lasting changes in synaptic efficacies at specific pathways and this phenomenon had not been previously verified, at a cellular level, in human synapses. In chapter 3, we set out to investigate the hippocampus' capacity to undergo long-lasting synaptic changes by probing the time window for STDP via extracellular stimulation and intracellular recordings.
3. How do connectivity and synaptic properties in the Fragile X and VPA models for mental retardation and autism translate into information processing impairments? We addressed these questions in chapters 4 and 5, by studying connectivity and synaptic properties in two distinct models for mental retardation and autism. In chapter 4 we examine the Fragile X model and verify whether the reported alterations in spine number and maturation influence connectivity rates, across two distinct developmental states and whether these changes are followed by alterations in the dynamics of excitatory synapses. In chapter 5 we test whether the reported findings on the VPA model for autism (Rinaldi et al., 2007) also extend to long term microcircuit plasticity (LTMP, Markram et al., 2011) and synaptic properties, when altered by the LTMP protocol.

TECHNICAL EXCURSUS: DETAILED DERIVATION OF THE TSODYKS-MARKRAM MODEL

We define a synaptic connection by its absolute amount of resources,

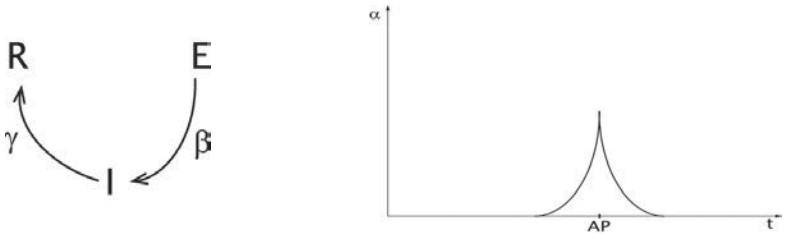
$$R + E + I = 1$$

Where R(recovered, ready-to-use), E(effective, in-use) and I(inactive, just-used, not-ready), denote the fraction of the limited resources available to the synapse or set of synapses. If all resources are consumed by a presynaptic AP, this would generate the maximal possible response, defined as the absolute synaptic efficacy (A_{SE}). Each presynaptic AP recruits a fraction of resources from the recovered state(R), transitioning to a state E that inactivates to a state I with a time constant τ_{in} and recovers back to state R with a time constant τ_{rec}.

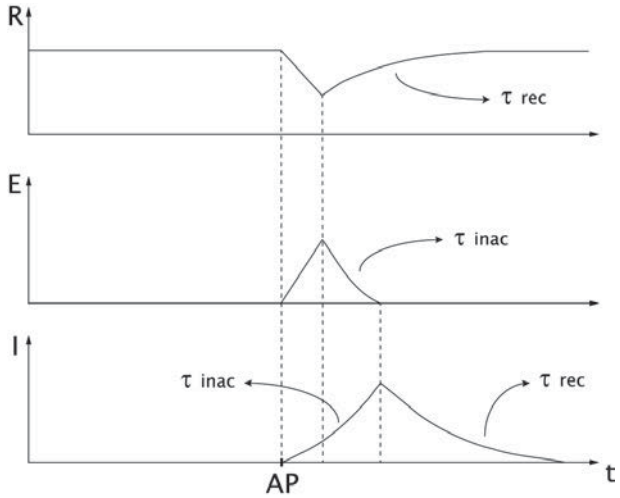


$$\begin{cases} \frac{dR}{dt} = -\alpha R + \gamma I \\ \frac{dE}{dt} = -\beta E + \alpha R \\ \frac{dI}{dt} = -\gamma I + \beta E \end{cases}$$

The biophysical processes that replenish those resources are slow and occur over a time scale τ_{rec} ($\alpha < \gamma = {}^{1}/_{\tau_{rec}} < \beta$). On the other hand, biophysical processes of activation, of ready-to-use (R) resources are very fast, infinitely fast, and occur only during an AP.

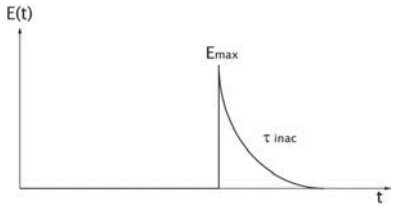


Biophysical processes related to inactivation are fast, $\beta = \frac{1}{\tau_{inac}} \gg \alpha$. The time course of the three time constants involved in the process described above can be better visualized by the following,



An excitatory postsynaptic response (EPSP) is assumed to be the area bellow E(t), during an AP, properly normalized by time.

If E(t) has the form,



we can say that $E(t) = E_{max} e^{-t/\tau_{inac}} \cdot H(t) \rightarrow E_{max} = \int_{-\infty}^{+\infty} E(t)\, dt \cdot \frac{1}{\tau_{inac}}$.

Let's simplify the model by the following assumptions:

i) α is instantaneous, $\alpha = U \cdot \delta(t - t_{AP})$, (exclusively depressing synapses)

ii) $\beta \gg \gamma \rightarrow \frac{1}{\tau_{inac}} \gg \frac{1}{\tau_{rec}}$, i.e. the time constant of inactivation is negligible compared to the time constant of recovery.

The system of equations, can be than simplified,

$$\tau_{inac}\frac{dE}{dt} = -E + \tau_{inac}U \cdot \delta(t - t_{AP}) \cdot R,$$

where $E_\infty = \tau_{inac} \cdot U \cdot \delta(t - t_{AP}) \cdot R$,at the steady state.

Note that, $I = 1 - R - E_\infty = 1 - R - \tau_{inac} \cdot U \cdot \delta(t - t_{AP}) \cdot R$, therefore,

$$\frac{dR}{dt} = \frac{1}{\tau_{rec}} \cdot I - U \cdot \delta(t - t_{AP}) \cdot R \rightarrow \frac{dR}{dt} = \frac{1 - R}{\tau_{rec}} - \frac{\tau_{inac} \cdot U \cdot \delta(t - t_{AP}) \cdot R}{\tau_{rec}} - U \cdot \delta(t - t_{AP}) \cdot R$$

Since $\tau_{inac}/\tau_{rec} \rightarrow 0$, we are left with one kinetic equation,

$$\frac{dR}{dt} = \frac{1 - R}{\tau_{rec}} - U \cdot \delta(t - t_{AP}) \cdot R.$$

And a condition to specify the peak amplitude of EPSPs,

$$E_{max} = \frac{1}{\tau_{inac}} \int_{-\infty}^{+\infty} E(t)dt = \frac{1}{\tau_{inac}} \cdot \tau_{inac} \cdot U \cdot R(t_{AP})$$

The net postsynaptic potential (as read from the soma), is scaled by the amount of resources in the effective state (E) and is, therefore, given by:

$$\overline{PSR} = A_{SE} \cdot R(t) \cdot U$$

where R(t) is the fraction of vesicles or resources available and U the probability of vesicle release, constant for depressing synapses. This phenomenological model can, in principle, account for biophysical mechanisms such as receptor desensitization and depletion of vesicles but, in a semi-quantitative way, i.e. offering elements for comparison, not absolute numbers.

For $t \neq t_{AP}$,

$$\frac{dR}{dt} = \frac{1 - R}{\tau_{rec}} \rightarrow R(t) = ke^{-t/\tau_{rec}} + 1$$

During an AP, $t = t_{AP}$

$$\int_{t_{AP}^-}^{t_{AP}^+} \frac{dR}{dt} = \int_{t_{AP}^-}^{t_{AP}^+} \frac{1 - R}{\tau_{rec}} - \int_{t_{AP}^-}^{t_{AP}^+} U \cdot R \cdot \delta(t - t_{AP})$$

By separating the variables, and neglecting the second term, for continuity, we obtain,

$$\int_{t_{AP}^-}^{t_{AP}^+} \frac{dR}{R} \cong -\int_{t_{AP}^-}^{t_{AP}^+} U \cdot \delta(t - t_{AP})dt$$

That results in

$$ln\frac{R(t_{AP}^{+})}{R(t_{AP}^{-})} \cong -U \rightarrow R(t_{AP}^{+}) \cong R(t_{AP}^{-})e^{-U},$$

if we mae U small (0<U<1), then, $e^{-U} \cong (1-U) \rightarrow R(t_{AP}^{+}) \cong R(t_{AP}^{-}) \cdot (1-U)$, this can be interpreted as the fraction of resources after "use". For example, if we "use" 70% of the available resources, then, $R(t_{AP}^{+}) = 0{,}3 \cdot R(t_{AP}^{-})$, after. i.e. $EPSP(t_{AP}) = A \cdot U \cdot R(t_{AP}^{-}) = 0{,}7 \cdot Before$.

The above reduction can then be translated into a numeric format, for iterative computation. In the case of a train of presynaptic spikes $\sum_{k=1}^{\infty} \delta(t-t_k)$,

$$\begin{cases} \dfrac{dR}{dt} = \dfrac{1-R}{\tau_{rec}} - \sum_{k=1}^{\infty} U \cdot R \cdot \delta(t-t_k) \\ EPSP_k = A \cdot U \cdot R(t_k^{-}) \end{cases}$$

Which integrated gives,

$$R(t) = K \cdot e^{-t-t_k/\tau_{rec}} + 1 \rightarrow R(t_{k+1}^{-}) = [R(t_k^{+}) - 1]e^{-t_{k+1}-t_k/\tau_{rec}} + 1 \rightarrow R(t_k^{+}) = R(t_k^{-}) \cdot (1-U),$$

leading to the following system,

$$\begin{cases} R(t_{k+1}^{-}) = R(t_k^{-})[1-U]e^{-t_{k+1}-t_k/\tau_{rec}} + 1 - e^{-t_{k+1}-t_k/\tau_{rec}} \\ EPSP = A \cdot U \cdot R(t_{k+1}^{-}) \end{cases}$$

The above derivation of the Tsodyks-Markram model is valid and works well for connections/synapses where depression dominates over facilitation. However, when the fraction U, of synaptic resources is not constant during a synaptic event, and represents an underlying process of facilitation.

The change in probability of release, described above, may reflect the kinetic scheme of calcium inside presynaptic boutons.

$$\begin{cases} \dfrac{du_{active}}{dt} = -\dfrac{u_{active}}{\tau_{facil}} + U \cdot \delta(t-t_{AP}) \cdot u_{recovered} \\ \dfrac{du_{recovered}}{dt} = \dfrac{u_{active}}{\tau_{facil}} - U \cdot \delta(t-t_{AP}) \cdot u_{recovered} \end{cases}$$

$$u_{active} + u_{recovered} = 1 \rightarrow u_{recovered} = 1 - u_{active}$$

Let's call $u_{active} \equiv u$, since we intend to use "its" active value, immediately after the time of the AP.

$$\frac{du}{dt} = -\frac{u}{\tau_{facil}} + (1-u) \cdot U \cdot \delta(t-t_{AP}),$$

that send us back to the system,

$$\begin{cases} \dfrac{dR}{dt} = \dfrac{1-R}{\tau_{rec}} - R \cdot u \cdot \delta(t-t_{AP}) \\ \dfrac{du}{dt} = -\dfrac{u}{\tau_{facil}} + (1-u) \cdot U \cdot \delta(t-t_{AP}) \end{cases}$$

Note that for $t \neq t_{AP}$, $\frac{du}{dt} = -\frac{u}{\tau_{facil}} \rightarrow u(t) = u(t_0)e^{-t-t_0/\tau_{facil}}$, during the AP,

$$\int_{t_{\overline{AP}}}^{t_{AP}^{+}} \frac{du}{dt} = -\int_{t_{\overline{AP}}}^{t_{AP}^{+}} \frac{u}{\tau_{facil}} + \int_{t_{\overline{AP}}}^{t_{AP}^{+}} U \cdot (1-u) \cdot \delta(t - t_{AP})$$

By separating the variables, and neglecting the second term, for continuity, we obtain,

$$\int_{u(t_{\overline{AP}})}^{u(t_{AP}^{+})} \frac{du}{1-u} \cong \int_{t_{\overline{AP}}}^{t_{AP}^{+}} U \cdot \delta(t - t_{AP})\, dt$$

resulting in

$$\frac{1-u(t_{AP}^{+})}{1-u(t_{\overline{AP}})} \cong e^{-U} \cong 1 - U \rightarrow u(t_{AP}^{+}) = (1-U)u(t_{AP}^{+}) + U,$$

Translating the above derived results into a numeric format, for iterative computation,

$$u(t_{k+1}^{+}) = u(t_{k+1}^{-}) \cdot (1-U) + U \rightarrow u(t_{k+1}^{-}) = u(t_k^{+})e^{-t_{k+1}-t_k/\tau_{facil}} \rightarrow u(t_{k+1}^{+})$$
$$= u(t_k^{+}) \cdot (1-U) \cdot e^{-t_{k+1}-t_k/\tau_{facil}} + U$$

So that $u(t_k^{+})$ appears in all of the previous equations.

$$\begin{cases} R(t_{k+1}^{-}) = R(t_k^{-})[1-u(t_k^{+})] \cdot e^{-t_{k+1}-t_k/\tau_{rec}} + 1 - e^{-t_{k+1}-t_k/\tau_{rec}} \\ EPSP_{k+1} = A \cdot u(t_{k+1}^{+}) \cdot R(t_{k+1}^{-}) \end{cases}$$

Having derived the model for both scenarios, namely, where depression dominates and where facilitation is present (U constant and variable, respectively), we are able to study a regime in which presynaptic spikes occur regularly, every T (i.e. firing rate is $f = 1/T$.

$$\begin{cases} R_{m+1=} R_m \cdot (1-u_m) \cdot e^{-T/\tau_{rec}} + 1 - e^{-T/\tau_{rec}} \\ u_{m+1} = u_m \cdot (1-U) \cdot e^{-T/\tau_{rec}} + U \\ EPSP_{m+1} = A \cdot u_{m+1} \cdot R_{m+1} \end{cases}$$

In a kind of dynamic equilibrium, where,

$$\begin{cases} R_{m+1} = R_m = R_\infty \\ u_{m+1} = u_m = u_\infty \end{cases}$$
$$\rightarrow \begin{cases} R_\infty = R_\infty(1-u_\infty)e^{-T/\tau_{rec}} + 1 - e^{-T/\tau_{rec}} \\ u_\infty = u_\infty(1-U)e^{-T/\tau_{facil}} + U \end{cases} \rightarrow u_\infty \left[1 - (1-U)e^{-T/\tau_{facil}}\right] = U$$

resulting in the steady state solution,

$$\begin{cases} u_\infty = \dfrac{U}{1-(1-U)e^{-T/\tau_{facil}}} \\ R_\infty = \dfrac{1-e^{-T/\tau_{rec}}}{1-(1-u_\infty)e^{-T/\tau_{rec}}} \end{cases}$$

For high frequencies, $T \ll 1$, $e^{-T/\tau_{rec}} \sim 1 - \frac{T}{\tau_{rec}}$, and replacing $f = \frac{1}{T}$

$$\rightarrow R_\infty \cong \frac{1}{f \cdot u_\infty \cdot \tau_{rec} + (1-u_\infty)}$$

Specifically, for $f \gg \frac{1}{u_\infty \tau_{rec}} \rightarrow R_\infty \cong \frac{1}{f \cdot u_\infty \cdot \tau_{rec}}$, for depressing synapses,

$$EPSP_\infty = \frac{A \cdot u_\infty}{f \cdot u_\infty \cdot \tau_{rec}} = \frac{A}{f \cdot \tau_{rec}}$$

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